

PENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

Date of mailing (day/month/year) 08 September 2000 (08.09.00)	To: Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/IB00/00165	Applicant's or agent's file reference XA 3400
International filing date (day/month/year) 05 January 2000 (05.01.00)	Priority date (day/month/year) 05 January 1999 (05.01.99)
Applicant RIDET, Jean-Luc et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

20 July 2000 (20.07.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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FENT COOPERATION TREA

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NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

		From the INTERNATIONAL BUREAU			
		To:			
		<p>BOUVET, Philippe Aventis Pharma S. A. Patent Department 20, avenue Raymond Aron F-92165 Antony FRANCE</p>			
Date of mailing (day/month/year) 08 September 2000 (08.09.00)					
Applicant's or agent's file reference XA 3400		IMPORTANT NOTIFICATION			
International application No. PCT/IB00/00165		International filing date (day/month/year) 05 January 2000 (05.01.00)			
<p>1. The following indications appeared on record concerning:</p> <p><input type="checkbox"/> the applicant <input type="checkbox"/> the inventor <input checked="" type="checkbox"/> the agent <input type="checkbox"/> the common representative</p>					
Name and Address <p>BOUVET, Philippe Rhone Poulenc Rorer S. A. Patent Department 20, avenue Raymond Aron F-92165 Antony France</p>		State of Nationality			
		State of Residence			
		Telephone No. 01 55 71 76 92			
		Facsimile No. 01 55 71 72 91			
<p>2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:</p> <p><input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence</p>					
Name and Address <p>BOUVET, Philippe Aventis Pharma S. A. Patent Department 20, avenue Raymond Aron F-92165 Antony France</p>		State of Nationality			
		State of Residence			
		Telephone No. 01 55 71 76 92			
		Facsimile No. 01 55 71 72 91			
<p>3. Further observations, if necessary:</p>					
<p>4. A copy of this notification has been sent to:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding-right: 20px;"> <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority </td> <td style="width: 50%;"> <input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other: </td> </tr> </table>				<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:
<input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> the designated Offices concerned <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> other:				

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	<p>Authorized officer Juan Cruz</p> <p>Telephone No.: (41-22) 338.83.38</p>
---	--



APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

Classification:	A3	(11) International Publication Number: WO 00/40699
		(43) International Publication Date: 13 July 2000 (13.07.00)

Application Number: PCT/IB00/00165 Priority Date: 5 January 2000 (05.01.00) 5 January 1999 (05.01.99) US <i>Designated States except US:</i> AVENTIS [FR]; Direction des brevets – Tri LE1 mond Aron, F-92165 Antony (FR). <i>(for US only): RIDET, Jean-Luc Dron 77/514, CH-1010 Lausanne (CH). [FR/FR]; 18, rue Charcot, F-75013</i>	(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 2 November 2000 (02.11.00)
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THEIR PREPARATION AND USES THEREOF

is an essentially pure preparation of human adult astrocytes, and a method of producing same. The purified treatment of neurodegenerative disorders or trauma to the central nervous system.

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INTERNATIONAL SEARCH REPORT

Item 1 and Application No

PCT/IB 00/00165

CT MATTER
C12N5/10 A61K48/00

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Classification (IPC) or to both national classification and IPC

(classification system followed by classification symbols)

n minimum documentation to the extent that such documents are included in the fields searched

ing the international search (name of data base and, where practical, search terms used)

IS, WPI Data, PAJ, SCISEARCH, BIOTECHNOLOGY ABS, CHEM ABS Data,

TO BE RELEVANT

, with indication, where appropriate, of the relevant passages

Relevant to claim No.

CORLINE J A ET AL:
 hment of human adult astrocyte
 derived from postmortem multiple
 and control brain and spinal
 ons: Immunophenotypical and
 l characterization."
 IF NEUROSCIENCE RESEARCH,
 no. 3, August 1997 (1997-08),
 -354, XP000864697
 US
 0-4012

1-6,
13-18

column 1, paragraph 1 -column 2,

2

column 1, paragraph 1 -page 348

-/-

ed in the continuation of box C.



Patent family members are listed in annex.

nento :

I state of the art which is not
 relevant

d on or after the international

ubstitution priority claim(s) or
 publication date of another
 on (as specified)
 disclosure, use, exhibition oro international filing date but
 aimed"T" later document published after the international filing date
 or priority date and not in conflict with the application but
 cited to understand the principle or theory underlying the
 invention"X" document of particular relevance; the claimed invention
 cannot be considered novel or cannot be considered to
 involve an inventive step when the document is taken alone"Y" document of particular relevance; the claimed invention
 cannot be considered to involve an inventive step when the
 document is combined with one or more other such docu-
 ments, such combination being obvious to a person skilled
 in the art.

"S" document member of the same patent family

is international search

Date of mailing of the International search report

26/07/2000

ISA
 Office, P.O. Box 5818 Patententeen 2
 12040, Tx. 31 651 epo rd.
 0-3016

Authorized officer

De Kok, A

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S CONSIDERED TO BE RELEVANT

Art. with indication, where appropriate, of the relevant passages	Relevant to claim No.
1135 A (UNIV NEW YORK) January 1994 (1994-01-20)	13, 14, 17-19, 23, 25-27, 29-31
line 16 - line 26 line 33 -page 10, line 10 , line 27 -page 13, line 30	1, 6
5631 A (UNIV CASE WESTERN RESERVE) 1991 (1991-05-16) , line 21 -page 49, line 27	13, 14
T AL.: "Human fetal astrocytes as a gene therapy vehicle for engineering biologically active nerve factor" GENE THERAPY, no. 3, January 1997 (1997-02-10), pages , XP000864703	1, 6 32
K US 1 document	
W ET AL.: "Gamma-interferon stimulates proliferation of adult human astrocytes in vitro and reactive gliosis in adult mouse brain in vivo" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., , August 1991 (1991-08), pages 20, XP002142263	13-18
NATIONAL ACADEMY OF SCIENCE. WASHINGTON., 027-8424	
n the application 16, column 2, paragraph 2 18; figure 2	1-6
IL ET AL: "Toward autologous ex vivo gene therapy for the central nervous system with human adult astrocytes" GENE THERAPY, , no. 2, January 1999 (1999-01-20), pages , XP002132470 1043-0342 1 document	1-32

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9401135	A 20-01-1994	AU	4664693 A	31-01-1994
WO 9106631	A 16-05-1991	US AU	5202120 A 6918891 A	13-04-1993 31-05-1991

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PATENT COOPERATION TREATY

PCT

REC'D 11 APR 2001

WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XA 3400	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB00/00165	International filing date (day/month/year) 05/01/2000	Priority date (day/month/year) 05/01/1999	
International Patent Classification (IPC) or national classification and IPC C12N5/06			
Applicant AVENTIS PHARMA S.A. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 20/07/2000	Date of completion of this report 06.04.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wimmer, G
	Telephone No. +49 89 2399 7347



INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/IB00/00165

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-33 as originally filed

Claims, No.:

1-32 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/IB00/00165

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 11, 28
	No: Claims 1-10, 12-27, 29-32

Inventive step (IS)	Yes: Claims
	No: Claims 1-32

Industrial applicability (IA)	Yes: Claims 1-32
	No: Claims

**2. Citations and explanations
see separate sheet**

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/IB00/00165

Re Item V

Reasoned statement under Art. 35(2) with regard to novelty, inventive step or industrial applicability.

The application does not meet the requirements of Art. 33 PCT since claims 1-10, 12- 27 and 29-32 are not novel, and claims 11 and 28 do not appear to contain an inventive step.

- 1) Reference is made to the following documents (the document numbering corresponds to their order of citation in the international search report):

D1: DE GROOT CORLINE J A ET AL: 'Establishment of human adult astrocyte cultures derived from postmortem multiple sclerosis and control brain and spinal cord regions: Immunophenotypical and functional characterization.' JOURNAL OF NEUROSCIENCE RESEARCH, vol. 49, no. 3, August 1997 (1997-08), pages 342-354, XP000864697 NEW YORK US ISSN: 0360-4012

D2: WO 94 01135 A (UNIV NEW YORK) 20 January 1994 (1994-01-20)

D4: LIN Q ET AL.: 'Human fetal astrocytes as an ex vivo gene therapy vehicle for delivering biologically active nerve growth factor' HUMAN GENE THERAPY, vol. 8, no. 3, 10 February 1997 (1997-02-10), pages 331-339, XP000864703 NEW YORK US

Novelty under Art. 33(2) PCT.

- 2) The method of claim 1 extends to the isolation or propagation of a population of astrocytes. Identical or similar methods have been disclosed repeatedly in the prior art. For instance, document D1 describes the isolation of astrocytes from adult human brain. The authors of D1 employ selective attachment of astrocytes to poly-L-lysine covered culture vessels, and removal of non-attached cells after 48 hours (page 344). This method leads to the recovery of a >95% pure astrocyte population as assessed by GFAP staining (page 347). Successive passages displayed even higher uniformity of population (>98%, page 347).

Therefore, claims 1-6, and claims 13-18 lack novelty.

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/IB00/00165

- 3) Likewise, the procedures described in D4 include the isolation of human embryonic astrocytes by the method of McCarthy and de Vellis. This method, which is commonly known in the field, utilizes the differential attachment of astrocytes and other cell types, and allows to obtain populations of >98% purity (see McCarthy and de Vellis (1980), J. Cell Biol. 85(3), 890-2).
The authors of D2 use thusly isolated human astrocytes for retrovirus-mediated transduction of murine β -NGF (Nerve Growth Factor) cDNA under the control of the MoMuLV LTR promoter.
Accordingly, the method of D4 constitutes subject-matter of present claims 7-9, 12, 19-21, 24-27, 29-30 and 32 which consequently lack novelty.
- 4) Although adenoviral gene delivery as claimed in claim 10 was not performed by the authors of D4, the document describes that besides retroviral transfer, also gene transfer through adenoviruses is "likely to be applicable" (pg. 337). Claims 10 and 22 are therefore not considered as being novel.
- 5) While the method of D2 includes the essential features of claim 11 (isolation of rat astrocytes by adhesion and removal of nonadherent cells, subsequent introduction of external DNA through calcium phosphate precipitation), the method differs insofar as astrocytes are isolated after a 5 to 6 day attachment period rather than after two days. Claim 11 can therefore be regarded as being novel.
- 6) As a consequence of the product-by-process definition of claim 23, known subject-matter falls within the terms of the claim. For example, extrachromosomal DNA introduced by viruses is not distinguishable from the same DNA introduced by transfection. Similarly, integrated or native chromosomal DNA is not distinguishable from transfected and chromosomally recombined DNA. Claim 23 is therefore not novel.
- 7) The use of an astrocyte population as an implant according to claim 31 has been frequently described (see e.g. the application itself, desc. pg. 2; D2, pg. 2, I.22-pg. 3, I. 25, and references therein). Claim 31 therefore lacks novelty.

Inventive Step under Art. 33(3) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/IB00/00165

- 8) Novel claims 11 and 28 differ from the prior art in minor points only.

The method of claim 11 is different to closest prior art, document D2, in the time of attachment of astrocytes only (see also sect. V.6). The IPEA does not see an unexpected result from the change from 5-6 days (D2) to 2 days of attachment. Furthermore, the skilled person would routinely investigate transfection (e.g. by calcium phosphate) of a human astrocyte culture as obtained through the method of D1, especially since D2 shows that rat astrocytes are transfecable by that method. Claim 11 therefore lacks an inventive step.

- 9) The use of DNA encoding an antisense-RNA, as referred to in claim 28, is a trivial alteration in a transfection method in general, and is not inventive.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference XA 3400	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/IB 00/00165	International filing date (<i>day/month/year</i>) 05/01/2000	(Earliest) Priority Date (<i>day/month/year</i>) 05/01/1999
Applicant AVENTIS PHARMA S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

- the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
- contained in the international application in written form.
 - filed together with the international application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

ASTROCYTES, THEIR PREPARATION AND USES THEREOF

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

- as suggested by the applicant.
- because the applicant failed to suggest a figure
- because this figure better characterizes the invention.

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

IB 00/00165

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N5/06 C12N5/10 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, SCISEARCH, BIOTECHNOLOGY ABS, CHEM ABS Data, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DE GROOT CORLINE J A ET AL: "Establishment of human adult astrocyte cultures derived from postmortem multiple sclerosis and control brain and spinal cord regions: Immunophenotypical and functional characterization." JOURNAL OF NEUROSCIENCE RESEARCH, vol. 49, no. 3, August 1997 (1997-08), pages 342-354, XP000864697 NEW YORK US ISSN: 0360-4012 abstract page 344, column 1, paragraph 1 -column 2, paragraph 2 page 347, column 1, paragraph 1 -page 348 --- -/-</p>	1-6, 13-18

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

11 July 2000

26/07/2000

Name and mailing address of the ISA

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De Kok, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/00165

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 01135 A (UNIV NEW YORK) 20 January 1994 (1994-01-20) page 9, line 16 - line 26 page 9, line 33 -page 10, line 10 page 10, line 27 -page 13, line 30 ---	13, 14, 17-19, 23, 25-27, 29-31
Y		1, 6
X	WO 91 06631 A (UNIV CASE WESTERN RESERVE) 16 May 1991 (1991-05-16) page 48, line 21 -page 49, line 27 ---	13, 14
Y		1, 6
X	LIN Q ET AL.: "Human fetal astrocytes as an ex vivo gene therapy vehicle for delivering biologically active nerve growth factor" HUMAN GENE THERAPY, vol. 8, no. 3, 10 February 1997 (1997-02-10), pages 331-339, XP000864703 NEW YORK US the whole document ---	32
X	YONG V W ET AL.: "Gamma-interferon promotes proliferation of adult human astrocytes in vitro and reactive gliosis in the adult mouse brain in vivo" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 88, August 1991 (1991-08), pages 7016-7020, XP002142263 NATIONAL ACADEMY OF SCIENCE. WASHINGTON., US ISSN: 0027-8424 cited in the application page 7016, column 2, paragraph 2 page 7018; figure 2 ---	13-18
A		1-6
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